REMARKS

Claims 1-5, 8-29, and 32-38 are pending after entry of this paper. Claims 1-5, 8-11, 13-15, 24, 27-29, 32-35, and 37-38 have been rejected. Claims 12, 16-23, 25-26, and 36 have been withdrawn and claims 6-7 and 30-31 have been cancelled without prejudice. Applicants reserve the right to pursue withdrawn and cancelled claims in a divisional or continuing application.

Reconsideration and withdrawal of the pending rejections in view of the following remarks are respectfully requested.

Response to Rejections under 35 U.S.C. §103

Claims 1-5, 8-11, 13-15, 24, 27-29, 32-35, and 37-38 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over WO 98/20020 to O'Donnell, et al. ("O'Donnell") in view of U.S. Patent No. 6,124,099 to Heckman, et al. ("Heckman"), and further in view of Marriott, et al. (*Biochemistry International* 26(5), 943-95, 1992) ("Marriott"). Specifically, the Examiner alleges that O'Donnell "teaches a method of acquiring data on the mass of a substrate fixed on a solid substrate (pg. 7, lines 1-6) that includes immobilizing nucleic acids on the substrate using photo cleavable linker moiety (pg. 33, lines 12-17)." (Office Action – pg 2). According to the Examiner, the O'Donnell reference also teaches "[i]rradiating the substance fixed on the substrate with a laser (pg. 34, lines 26-28) ... and analyzing the mass spectrum of the substance which is brought in an unfixed state by disconnecting the partial structure by the irradiation of light (Fig. 17, pg. 25 lines 7-29)." (Office Action – pg 3). The Examiner admits that O'Donnell does not teach a compound represented by formula II, which is allegedly taught by Heckman. The Examiner contends that since the linker of Formula II has very long term stability in the dark, it would have being obvious to use it in the process of

O'Donnell. Furthermore, the Examiner admits that the combination of O'Donnell and Heckman does not teach a photo cross-linking agent that is also photocleavable, which is allegedly made obvious in view of Marriott. (Office Action – pg. 4). Applicants respectfully disagree with Examiner's analysis and conclusion.

Contrary to the Examiner's contention, O'Donnell alone, or in combination with Heckman and Marriott, does not disclose each and every step of the claimed method. O'Donnell teaches a process of immobilizing nucleic acids using a bifunctional cross-linking agents, *e.g.*, SIAB, on to an insoluble surface. O'Donnell further teaches the analysis of target DNA disconnected from the immobilized DNA by the conditions of mass spectroscopy (Fig 17 cited by the Examiner; See Example 5). The target DNA as disclosed in Fig. 17 is prepared according to Example 1, where the target DNA is hybridized with the immobilized DNA. The irradiation of the hybridized double stranded DNA caused the annealed strand to detach from the immobilized DNA strand and observed in the mass spectrum. (See pg. 75, lns. 25-30). In other words, the DNA strand analyzed by mass spectroscopy in O'Donnell was not the immobilized DNA as alleged by the Examiner. "It was determined that the wafer-conjugated strand was not desorbed thus the iodoacetamido linkage was stable enough to withstand the laser and remain intact." (pg. 76, lns. 2-4). Therefore, the Examiner is erroneous in alleging that O'Donnell teaches "[i]rradiating the substance fixed on the substrate with a laser (pg. 34, lines 26-28) … and analyzing the mass spectrum of the substance which is brought in an unfixed state by disconnecting the partial structure by the irradiation of light (Fig. 17, pg. 25 lines 7-29)." (Office Action – pg 3; emphasis added). Applicants assert that the compound analyzed by mass spectroscopy in O'Donnell is not the immobilized DNA strand, but the annealed DNA strand (complementary strand in double-stranded DNA), which detaches under mass spectroscopy

conditions. For this reason alone, applicants assert that the claimed method is not made obvious by the combination of O'Donnell, Heckman, and Marriott.

However, assuming for the sake of argument, that O'Donnell teaches the steps alleged in the Office Action at pages 2-3, the combination of O'Donnell, Heckman, Marriott still does not make obvious the claimed invention. The Examiner admits that O'Donnell does not teach a compound represented by formula II, which is allegedly taught by Heckman. (Office Action – pg. 3). In response to the applicant's arguments of April 21, 2008, the Examiner contends that O'Donnell teaches nitrobenzyl group as a photocleavable group at pg. 34, lines 3-9 and the nitrobenzene compounds disclosed in Heckman would be obvious alternatives (Office Action – pg. 19), merely because Marriott discloses a variant of nitrobenzene that can be photo-cleaved. Applicants respectfully disagree.

While nitrobenzyl group is widely used in organic synthesis as a protecting group and a cleavable linker, the efficiency of the photocleavage step depends on many factors including the efficiency of light absorption by the nitrobenzyl moiety, the efficiency of the primary photochemical step, and the efficiency of the secondary thermal processes that lead to the final cleavage process. Merely because the compound has a nitrobenzyl group does not make it a compound suitable in the process taught by O'Donnell. There are many variations possible with a nitrobenzyl group, *i.e.*, broad genus. As the Examiner is well aware, a genus does not teach species within the genus unless one of ordinary skill in the art is able to "at once envisage" the species within the genus (MPEP 2131.02). In fact, O'Donnell does not even disclose a generic chemical formula that would encompass the claimed compound represented by Formula II. (See Formula I and II at pg. 39 of O'Donnell). Nevertheless, the Examiner relies on disclosure of Heckman that teaches the placement of the photo cross-linking agent at specific

internal positions within a ribonucleotide and the use of these photoactive ribonucleotides to identify novel, sequence-specific target molecules. (Heckman, Col. 2, lns. 35-41). Specifically, Heckman teaches that the cross-linking occurs at UV wavelength > 300 nm. (Col. 8, lines 38-40). On the other hand, O'Donnell and Marriott teach that photo-induced cleavage occurs at around 350 nm (O'Donnell; page 34; Marriott; pg. 944).

If, for argument's sake, a skilled artisan combines Heckman with O'Donnell and Marriott, a skilled artisan would be perplexed about what will happen under the UV irradiation, *i.e.*, cross-link or desorb, because two alleged photoreactions would be competing against each other. In other words, if a skilled artisan attempted to prepare a system disclosed in O'Donnell using the cross-linking agent taught by Heckman, a skilled artisan would first attach the Heckman linker to the insoluble support, second, add the DNA to be immobilized and third irradiate the composition to create an immobilized DNA on the insoluble support as taught by Heckman. However, in view of Marriott, the third step would not work because during the irradiation step the DNA would desorb from the linker, thereby, precluding a skilled artisan from making an immobilized DNA on the insoluble support.

Applicant asserts that the Examiner must view the cited art as a whole and cannot ignore the teachings of Heckman. In fact, substituting the linkers with the Heckman linker as proposed by the Examiner, will substantially change the invention of O'Donnell and would make it inoperable because, according to Heckman, the succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate compound functions as a photo-induced cross-linker. MPEP 2143.01 clearly states that the proposed modification of the prior art cannot change the principle of operation of the primary reference or render the reference inoperable for its intended purpose.

Regardless of what the Marriott reference teaches, the Examiner's proposed modification of O'Donnell's immobilized DNA system would make the cross-linker inoperable for its intended purpose, which is a photocleavable linker, and can not be used as a basis for a rejection. (See MPEP 2143.01). The Examiner is invited to provide any evidentiary support without employing impermissible hindsight to demonstrate how photo-induced cross-linking and photo induced cleavage at the same wavelength could or would work, in particular with respect to the succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate compound disclosed in Heckman. Since Heckman uses this compound in photo-induced crosslinking, Heckman, in fact, teaches away from the claimed invention. As such, it would not have been obvious to use the photo-induced cross-linking agent of Heckman as means of connecting a substance to a substrate by a photocleavable linker for use in mass spectroscopy.

Accordingly, O'Donnell, Heckman, and Marriot whether alone or in combination fail to teach, disclose, or suggest a method of "using a structure including a partial structure to be disconnected by light to fix the substance on the substrate," wherein a nitrobenzene-containing structure is "constructed with a compound represented by the following formula II" as recited in applicant's claim 1. Applicant respectfully submits that independent claim 1 is patentably distinct from O'Donnell, Heckman, and Marriott for at least these reasons. Since independent claims 15, 24, and 27 also include the limitation wherein the nitrobenzene is "constructed with a compound represented by the following formula II" they are asserted to be patentably distinct for at least similar reasons. Dependent claims 2-5, 8-11, 13-14, 28-29, 32-35, and 37-38 are also in condition for allowance for at least similar reasons. The Section 103(a) obviousness rejection should therefore be withdrawn. Applicant submits that all of the pending claims are now

allowable for the above reasons and early, favorable action in that regard is respectfully requested.

CONCLUSION

Based on the foregoing amendments and remarks, the applicant respectfully request reconsideration and withdrawal of the pending rejections and allowance of this application. The applicant respectfully submits that the instant application is in condition for allowance. Entry of the amendment and an action passing this case to issue is therefore respectfully requested. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided. Favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 1232-5564.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 1232-5564.

Respectfully submitted,
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Dated: December 2, 2008 By: _____

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